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# Double-blind randomized controlled trial to determine extent of amnesia with midazolam given immediately before general anaesthesia

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**Background.** Anterograde, but not retrograde, amnesia has been demonstrated following midazolam administration. However, there have been no studies investigating whether or not immediate retrograde amnesia can be produced with midazolam.

**Methods.** After ethics committee approval and consent, 40 adult patients undergoing surgery and general anaesthesia were randomly allocated to one of four groups: midazolam 2 mg, midazolam 5 mg, midazolam 10 mg or control (normal saline). Measurements were made from 12 min prior to induction of anaesthesia, and the study drug was administered 8 min prior to induction of anaesthesia. Midazolam effects were measured using visual recognition of posters, recall of specific events, bispectral index (BIS) and sedation visual analogue score.

**Results.** Recognition and recall rates were similar between groups up until the time of study drug administration, with no evidence of retrograde amnesia (all $P>0.3$). There was a dose-dependent deterioration in visual recall ($P=0.002$), event recollection ($P<0.001$), BIS ($P<0.001$) and sedation score ($P<0.001$) following i.v. midazolam when compared with control.

**Conclusions.** We found no evidence that i.v. midazolam 2–10 mg produces immediate retrograde amnesia. Midazolam causes anterograde amnesia in a dose-responsive manner.

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Midazolam is a sedative drug with amnesic properties.[1–10] Previous studies have found that anterograde, but not retrograde, amnesia can be demonstrated with midazolam.[7–9] However, the time period in which memory is studied is typically 1 h or more prior to drug administration. This time frame does not adequately address the period of most clinical relevance to anaesthetists, and indeed the period where retrograde amnesia could provide some benefit for the patient, i.e. the period immediately prior to midazolam administration with the patient in the operating suite. There is some evidence that sedative drugs can induce retrograde amnesia in animals, at least with high-dose (75 mg $kg^{-1}$) propofol,[10 11] and so it is possible that midazolam could induce immediate retrograde amnesia.

However, there is no information regarding the reliability, immediacy of onset and dose response of the amnesic properties of i.v. midazolam in humans, particularly in the more commonly used clinical dose range of 1–5 mg. Nor are there any studies investigating the presence or absence of immediate retrograde amnesia with midazolam in this setting, i.e. the brief (1–10 min) period immediately preceding i.v. administration at a time when memory processing and organization is thought to occur.[1 2 5] Such an effect could provide protection against possible awareness if, for example, purposeful movement or depth of anaesthesia monitoring indicated wakefulness during surgery. Such a drug could also be used in the unfortunate scenario where a patient experiences a painful or distressing event in the immediate preinduction period, such as inadvertent administration of a muscle relaxant prior to induction of anesthesia, or repeated or distressing i.v. cannulation.

The primary aim of this study was to characterize the extent of immediate retrograde amnesia following i.v. midazolam administered before induction of general anaesthesia. Secondary aims were to determine the timing and dose response of its amnesic effects.

## Methods

After institutional ethics committee approval and written informed consent, 40 adult patients (ASA I or II) undergoing surgery and general anaesthesia were included in this prospective double-blind randomized study. The exclusion criteria were age >60 yr, weight <50 kg or >100 kg, protease inhibitor therapy, recent (<24 h) sedative or tranquilizer administration, visual or hearing impairment, known or suspected memory impairment or known or suspected psychiatric disturbance. No sedative premedication was used. The intraoperative conduct of anesthesia was left to the discretion of the anaesthetist, with the exception that administration of ketamine, clonidine or benzodiazepines was excluded.

A trained assistant, not involved in the provision of anaesthesia, prepared the study medication according to a computer-generated randomization code detailed in sequentially numbered opaque sealed envelopes. There were 10 patients in each of four groups: midazolam 2 mg, midazolam 5 mg, midazolam 10 mg and control (normal saline). Study personnel, anaesthetists and patients were blinded to group identity. The study was performed in the operating theatre, with measurements commencing 12 min prior to induction of anaesthesia. The study drug was administered as a 10 ml i.v. bolus at 8 min prior to induction of anaesthesia; this was defined as time zero ($T_0$). At predetermined intervals the patient underwent testing as described below.

Induction of anaesthesia commenced from time $T_{+8\ min}$, and consisted of i.v. propofol titrated to loss of consciousness and maintenance with sevoflurane/nitrous oxide. Choice of muscle relaxant was left to the discretion of the anaesthetist. The only opioids used were fentanyl and/or morphine. No further data collection occurred until the time of postoperative testing when recovery from anaesthesia had occurred, at least 4 h following discharge from the recovery room.

Memory tests were used to evaluate explicit recall; there were no tests of implicit (subconscious) memory. Each patient was shown a series of identical posters and underwent identical events at specific time points:

### *Poster recognition and recall*[1679]

Visual recognition and recall were tested using 12 laminated A4 posters, each with a unique easily recognizable simple image: PRE1, shark; PRE2, turtle; PRE3, brick wall; PRE4, two dice; PRE5, top hat; PRE6, trophy. Six images were designated as preoperative images (PRE1–PRE6); these were shown to each patient at $T_{-4\ min}$ (PRE1), $T_{-2\ min}$ (PRE2), $T_{-1\ min}$ (PRE3), $T_0$ (PRE4), $T_{+4\ min}$ (PRE5) and $T_{+8\ min}$ (PRE6). Patients were asked to identify each poster at the time of visual presentation. If a patient was deeply sedated, he or she was gently shaken and reminded to look at the posters. In addition, there were six further images that were shown only at the postoperative interview (POST7–POST12), as controls in order to identify spurious recollections. The order of poster viewing was standardized: preoperatively, sequential PRE1–6; postoperatively, PRE1, POST7, PRE2, POST8, POST9, PRE3, PRE4, POST10, PRE5, PRE6, POST11, POST12.

### *Patient recall of procedure or event*

One of the secondary aims of the study was to identify whether i.v. midazolam was able to improve a patient's experience in the operating suite by limiting recall of unpleasant events. Thus specific events and their recall were incorporated into the study. We judged that emotive or meaningful memories would be more readily recalled. In addition to any events spontaneously recalled by the patient, we specifically used the following events at these time points:

$T_{-4\ min}$: intravenous cannulation
$T_{-2\ min}$: patient moved from trolley to operating table
$T_{-1\ min}$: patient asked to poke out their tongue
$T_0$: preoxygenation commenced via mask (until induction)
$T_{+4\ min}$: patient asked to squeeze eyes shut and then open them
$T_{+8\ min}$: patient shown a 20 ml syringe containing propofol and told: 'You are about to go off to sleep with this milky solution'

At the postoperative assessment patients were asked if they could recall any of the above events. We included an additional fictitious event, a finger-prick test, as a control event in order to identify spurious reporting by the patient.

### *Sedation level*

Upon entering the operating theatre, a bispectral index (BIS) monitoring electrode was placed according to the manufacturer's instructions (Aspect Medical Systems Inc., Newton, MA, USA) and BIS monitoring was used to quantify the extent of sedation produced by the study drug. BIS was monitored continuously, and recordings were made at $T_{-4\ min}$, $T_{-2\ min}$, $T_{-1\ min}$, $T_0$, $T_{+4\ min}$ and $T_{+8\ min}$. In addition, a 100 mm visual analogue scale (VAS) was used. The VAS ranged from 'totally awake' (=0) to 'asleep' (=100). A VAS score corresponding to the degree of sedation of the patient was noted at times $T_{-4\ min}$, $T_{+4\ min}$ and $T_{+8\ min}$, as well as during the postoperative assessments. This was a subjective assessment and was performed by both the patient and the investigator. If patients were too drowsy to complete their VAS, it was scored as 100.

### *Sample size and statistical analysis*

The chosen sample size was guided by previous studies.[34679] We estimated a reduction in the mean (SD)

**Table 1** Patient and surgery characteristics. Data are median (interquartile range) or number, unless otherwise stated. VAS, 100 mm visual analogue score

| Characteristic | Control group (*n*=10) | Midazolam groups | | |
|---|---|---|---|---|
| | | 2 mg (*n*=10) | 5 mg (*n*=10) | 10 mg (*n*=10) |
| Age (yr) | 37 (31–45) | 35.5 (32–43) | 32 (30–44) | 38 (30–52) |
| Weight (kg) | 68 (57–81) | 77 (61–91) | 71 (62–81) | 74 (69–79) |
| Height (cm) | 165 (159–180) | 174 (162–189) | 171 (167–180) | 167 (165–171) |
| Physical status | | | | |
| ASA I | 9 | 6 | 9 | 6 |
| ASA II | 1 | 4 | 1 | 4 |
| Type of surgery | | | | |
| General | 6 | 8 | 1 | 4 |
| Orthopaedic | 2 | 1 | 4 | 3 |
| Other | 2 | 1 | 5 | 3 |
| Duration of operation (min) | 53 (36–114) | 67 (27–118) | 73 (38–127) | 53 (41–137) |
| Sedation VAS at baseline (mm) | | | | |
| Patient rating | 0 (0–5) | 1.5 (0–13) | 0 (0–12) | 0 (0–14) |
| Investigator rating | 0 (0–0) | 0 (0–1) | 0 (0–0) | 0 (0–0) |
| Bispectral index at baseline | 97 (96.5–98) | 97 (94.3–98) | 97 (96.5–98) | 97.5 (96.8–98) |
| Propofol induction dose (mg) | 200 (165–200) | 190 (158–200) | 180 (123–200) | 130 (93–200) |
| Total dose of morphine (mg) | 10 (6–10) (*n*=10) | 10 (5–10) (*n*=9) | 8 (0–10) (*n*=7) | 7.5 (0–10) (*n*=7) |
| Total dose of fentanyl (median) (μg) | 100 (*n*=1) | 100 (*n*=4) | 200 (*n*=3) | 100 (*n*=3) |
| Sevoflurane (end-tidal %) | 1.4 (1.0–2.0) | 1.4 (1.2–1.7) | 1.3 (0.9–1.9) | 1.1 (0.9–1.5) |
| Nitrous oxide (end-tidal %) | 63 (60–65) | 60 (60–65) | 60 (60–60) | 60 (50–60) |

number or posters recalled from 3.0 (1.2) to 1.0 (1.2). To account for the possibility of non-normality we further increased the sample size by 10%. With a type I error of 0.05 and a type II error of 0.2, the required number was calculated at 10 patients per group (Clinical Trials Design Program V1.0, Biosoft, Cambridge, UK). Despite basing our sample size estimation on numerical data, we chose to analyse the trend in the proportion of recollected items at each time point across the groups using general linear models to test for a midazolam dose effect. A 50% reduction in recollection rates between two groups (from 95% to ⩽50%) requires 15 patients per group (one-sided exact test, α 0.05) to have at least 80% power. Rates were compared using $\chi^2$ or Fisher's exact test as appropriate. Associations were measured using Spearman rank correlation (ρ). All analyses were done with SPSS for Windows V11.1. A two-sided *P* value <0.05 was considered statistically significant.

## Results

All patients enrolled completed the study. The patient and surgery characteristics and the anaesthetic and opioid drug usage were similar between groups (Table 1). There were four patients with an investigator-rated VAS score of 100 at $T_{+4\ min}$, and two at $T_{+8\ min}$; all were in the midazolam 10 mg group. The patient-rated (*P*=0.63) and investigator-rated (*P*=0.69) sedation VAS scores at the time of the postoperative interview were similar between groups. No patient incorrectly identified any of the six postoperative-only posters nor the fictitious finger-prick when questioned at the postoperative interview.

### *Poster recall (Table 2)*

There was no evidence of retrograde amnesia, with no significant differences in the rates of recall up to the time of study drug administration (at times $T_{-4\ min}$, $T_{-2\ min}$ and $T_{-1\ min}$) (*P*>0.99). After study drug administration each midazolam group recognized fewer posters than the control group, and a significant dose-response effect demonstrated (*P*=0.002) (Table 2).

**Table 2** Visual recall: number of patients in each group that recognized each poster. Six posters were shown to each patient, four before (PRE1, PRE2, PRE3, PRE4) and two after (PRE5, PRE6) administration of the study drug

| Poster | Timing in relation to study drug administration (min) | Control group (*n*=10) | Midazolam groups | | | *P*-value |
|---|---|---|---|---|---|---|
| | | | 2 mg (*n*=10) | 5 mg (*n*=10) | 10 mg (*n*=10) | |
| *Test for retrograde memory* | | | | | | |
| PRE1 | −4 | 10 | 10 | 10 | 10 | >0.99 |
| PRE2 | −2 | 10 | 10 | 10 | 10 | >0.99 |
| PRE3 | −1 | 10 | 9 | 9 | 10 | 0.55 |
| PRE4 | 0 (study drug given) | 7 | 10 | 9 | 6 | 0.10 |
| *Test for anterograde memory* | | | | | | |
| PRE5 | +4 | 8 | 2 | 0 | 1 | <0.0005 |
| PRE6 | +8 | 8 | 4 | 1 | 0 | 0.001 |

### *Event recall (Table 3)*

The retrograde event recall rates were not significantly different between groups (*P*>0.99). Anterograde event recall demonstrated a significant dose effect of midazolam (*P*<0.001) (Table 3). In the 5 mg and 10 mg groups, >50% remembered mask preoxygenation which commenced at $T_0$ and continued until induction of anaesthesia.

Of interest, one patient undergoing knee arthroscopy had a thigh tourniquet inadvertently inflated to 300 mm Hg at about 4 min after study drug administration (4 min before induction of anaesthesia) and complained of extreme discomfort. This patient had no recall of this event postoperatively. At the conclusion of the trial, when the results

**Table 3** Event memory: number of patients in each group who recalled a specifically timed event

| Event | Timing in relation to study drug administration (min) | Control group ($n=10$) | Midazolam groups | | | *P*-value |
|---|---|---|---|---|---|---|
| | | | 2 mg ($n=10$) | 5 mg ($n=10$) | 10 mg ($n=10$) | |
| I.V. cannulation | −4 | 10 | 10 | 10 | 10 | >0.99 |
| Move onto operating table | −2 | 9 | 10 | 10 | 10 | 0.38 |
| Asked to poke out tongue | −1 | 10 | 10 | 10 | 10 | >0.99 |
| Mask preoxygenation | 0 | 10 | 10 | 4 | 3 | <0.0005 |
| Squeeze eyes shut | +4 | 9 | 0 | 0 | 0 | <0.0005 |
| Shown propofol induction syringe | +8 | 10 | 3 | 0 | 0 | <0.0005 |
| Finger-prick (did not occur) | – | 0 | 0 | 0 | 0 | >0.99 |

**Table 4** Sedation levels before and after administration of study drug, as measured by bispectral index (BIS) and a 100 mm visual analogue scale (VAS). Data are mean (SD) or median (interquartile range). *$P$ values calculated for a midazolam dose effect using generalized linear models. †$P$ value calculated for repeated measures over the preceding four time points

| | Control group | Midazolam groups | | | *P*-value* |
|---|---|---|---|---|---|
| | | 2 mg | 5 mg | 10 mg | |
| BIS 4 min before study drug | 96.5 (2.12) | 95.7 (3.30) | 96.3 (2.71) | 97.3 (1.16) | |
| BIS 2 min before study drug | 96.3 (2.41) | 96.0 (2.49) | 96.2 (2.57) | 96.8 (1.14) | |
| BIS 1 min before study drug | 96.0 (2.31) | 96.0 (1.94) | 96.5 (1.84) | 97.1 (1.20) | |
| BIS at the time of study drug | 95.3 (2.83) | 94.6 (3.53) | 94.8 (4.71) | 96.9 (0.74) | 0.45† |
| BIS 4 min after study drug | 97.0 (88–98) | 87.5 (81–94) | 82.5 (75–97) | 71.0 (66–86) | 0.001 |
| BIS 8 min after study drug | 97.0 (92–98) | 92.0 (83–96) | 88.0 (82–97) | 74.0 (71–83) | <0.0005 |
| Sedation VAS (mm) | | | | | |
| 4 min after study drug | | | | | |
| Researcher rating | 9.5 (0–16) | 17.0 (15–40) | 37.5 (19–76) | 56.0 (38–100) | <0.001 |
| Patient rating | | 24 (14–50) | 42 (13–55) | 78 (30–100) | 0.004 |
| 8 min after study drug | | | | | |
| Researcher rating | 6 (0–20) | 16.5 (6–36) | 36 (14–65) | 53.5 (37–94) | <0.001 |
| Patient rating | 10 (2–24) | 21 (7–61) | 53 (17–67) | 57 (39–100) | 0.011 |

were unblinded, it was found that this patient was in the midazolam 10 mg group.

### *Sedation level and BIS*

There was no difference in BIS scores up to the time of study drug administration. From this time onwards the midazolam groups had a dose-responsive increasing effect on BIS ($P<0.001$) (Table 4). There was a correlation between the BIS scores (at $T_{+4\ min}$, with $T_{+8\ min}$ being similar) and event recall: $T_{-2\ min}$, $\rho=-0.02$, $P=0.89$; $T_0$, $\rho=0.53$, $P<0.001$; $T_{+4\ min}$, $\rho=0.51$, $P=0.001$; $T_{+8\ min}$, $\rho=0.56$, $P<0.001$.

As expected, baseline sedation scores were very low in each group. After study drug administration, sedation scores increased significantly in patients receiving midazolam ($P<0.001$) (Table 4). Of interest, the patients' own assessments of their levels of sedation were consistently higher than the researcher ratings.

## Discussion

This study could not demonstrate any measurable degree of retrograde amnesia for visual or event memory with i.v. midazolam 2–10 mg, when administered prior to general anesthesia. We did identify the ability of i.v. midazolam to produce anterograde amnesia, as has been demonstrated previously.[1–9 12] In addition, we identified a clear dose–response relationship.

However, there was a significant difference in the recall of events at the time of midazolam administration with higher doses of midazolam (5 and 10 mg) resulting in a lower recall rate of the current event, mask preoxygenation. This event was timed to occur simultaneously with the administration of midazolam, but continued until induction of anaesthesia. Given that this occurred before a meaningful effect site concentration of midazolam could have been achieved, it suggests a possibility of immediate retrograde amnesia. However, if such an effect exists, it must truly be near-instantaneous as it does not affect memory of events in the minutes before midazolam administration. Almost all patients were able to recollect events at 1, 2 and 4 min prior to midazolam administration. In our study we chose to include the time period immediately prior to the administration of the drug, which is a time period not tested in the literature to date and, indeed, the time period most likely to be useful if any degree of retrograde amnesia was to be found.

Our study also confirmed that the level of sedation, as measured by BIS and VAS, increases following

administration of midazolam in a dose-dependent manner. This finding, although not new, illustrates a strong point of our study design in that we achieved effective sedation levels typical of routine practice. The extent of sedation as measured by BIS was correlated with anterograde amnesia as measured by event recall. Sedation will affect consciousness of current events and can be expected to impair memory processing.[5] Some of the midazolam-induced anterograde amnesia demonstrated in this study could be explained by this mechanism. The increased amnesia demonstrated in the time period after study drug administration was closer to the time of induction when propofol was administered. There is some evidence that, at very high doses (75 mg $kg^{-1}$), propofol can induce retrograde amnesia in rodents,[10 11] and so it is theoretically possible that it could have contributed to the amnesic effects demonstrated in the immediate preinduction period. It should also be recognized that midazolam administration during anaesthesia may be influenced by amnesic effects of propofol or other coadministered hypnotic drugs.[13]

More than 20 different tests have been reported in the literature for measuring an amnesic effect of midazolam.[1–9 12] The tests chosen in our study have been used widely and are consistently reliable.[1 3 4 6 7 9] No patient recollected any of the postoperative-only posters or the fictitious finger-prick. This indicates a lack of spurious reporting and supports the reliability of the memory-testing procedures. A few patients in the control group could not recall some events or posters, which illustrates that some of the measured amnesia could be due to inattention or inability to retrieve memory; this can be attributed to the study environment (in the operating theatre, immediately before induction of anaesthesia). Naturally these factors affect all patients and it highlights the importance of including a control group in such research. We studied 10 participants in each group; it remains possible that we could have missed a small effect of midazolam-induced retrograde amnesia, but we believe that if such an effect exists, it would have little, if any, clinical utility. Our study sample size calculation was partly guided by previous studies but, because each had used different methodologies, the final estimates were based on what we considered to be a clinically important difference. We chose to analyse the midazolam dose effect using general linear models, but such an approach did not allow us to estimate study power accurately. Our study did not take into consideration all types of memory, as it would have been impractical to perform all the necessary tests simultaneously. In particular, it is important to differentiate explicit recall from implicit recall detected by special testing, and to differentiate recognition memory from other sensory modalities (hearing, touch and olfaction).[5] We chose to focus on visual and event explicit recall and visual recognition memory. We did not include a test of auditory memory, which would be particularly useful in the context of awareness prevention during surgery, since heard voices and sounds are commonly involved in awareness reports.

It is a common belief that the amnesic properties of midazolam can be used to prevent or treat suspected awareness.[12] However, the dose of midazolam required to achieve such an effect had not been previously studied, and it is known that awareness can still occur in patients who have received midazolam.[14 15] Our study results indicate that midazolam cannot be used to reliably produce retrograde amnesia, even of very short duration. Immediate anterograde amnesia can be achieved, and this may be of some clinical utility in reducing the risk of awareness at specific times during surgery.

## Conclusion

We found that i.v. midazolam up to a dose of 10 mg does not reliably produce any significant degree of clinically relevant retrograde amnesia. However, i.v. midazolam produces immediate onset anterograde amnesia at doses of 5 and 10 mg in adult patients. This may be useful in preventing explicit recall of perioperative events.

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